

# Small molecule discovery

**NCATS** Improving Health Through Smarter Science

## Small Molecule Discovery in Oncology and Beyond: Challenges and Opportunities

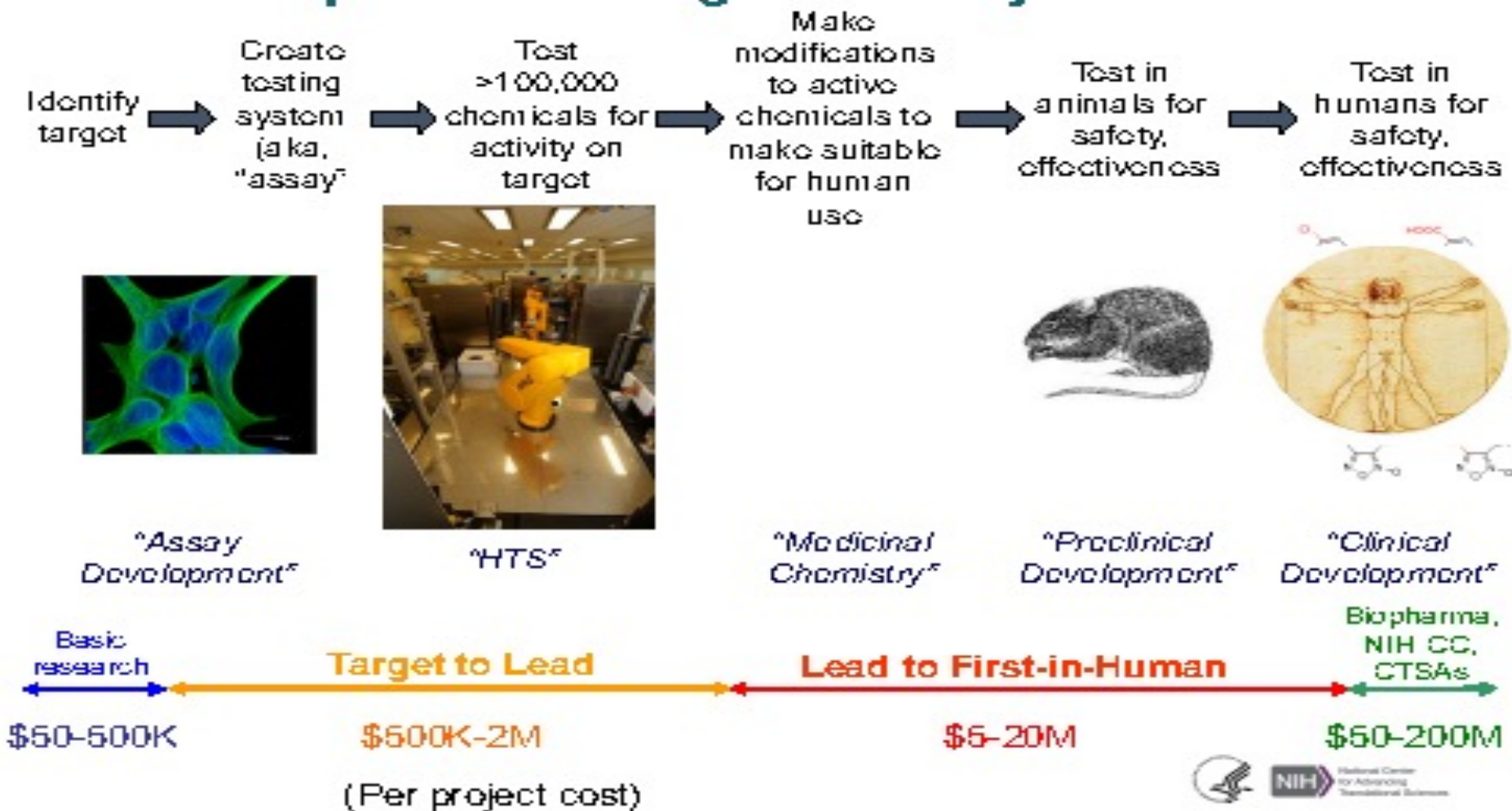
Anton Simeonov, Ph.D.

*Scientific Director, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH)*

**TRACO Lecture**  
**September 27, 2021**

# Drug Discovery Process

## Steps in the Drug Discovery Process



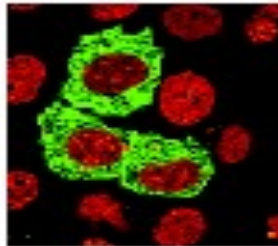
# Range of screening assays

## Range of Screening Assays

*Extent of reductionism* →

**Phenotype**

*(Image-based  
HCS, GFP, etc)*



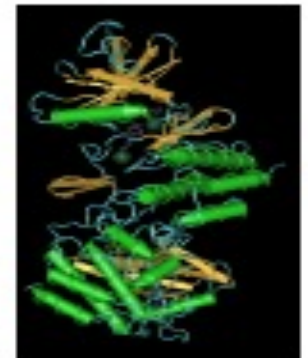
**Pathway**

*(Reporters, e.g., luciferase,  $\beta$ -lactamase)*



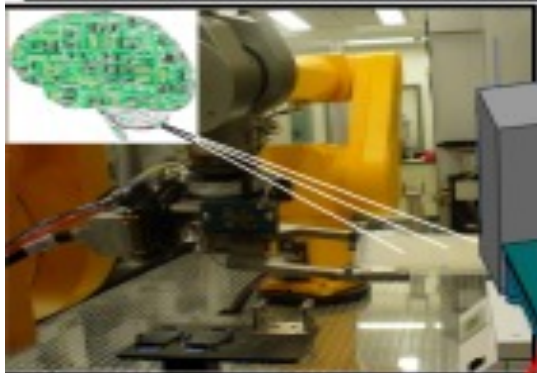
**Protein**

*(Enzyme readouts, interactions, etc)*



# High throughput screening

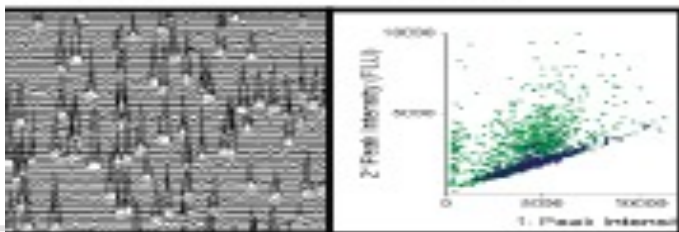
## Robotics & Informatics



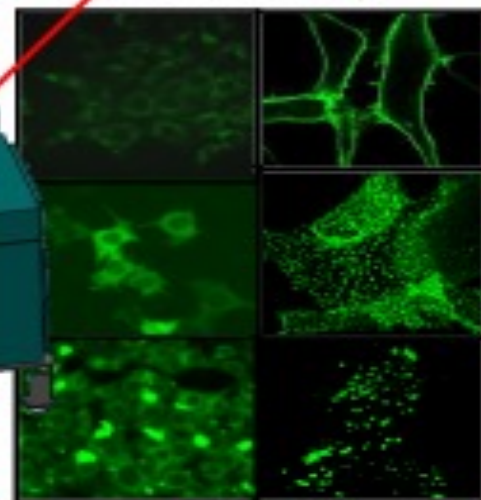
## Microliter Dispensing



## Laser Cytometry



## Microscopy



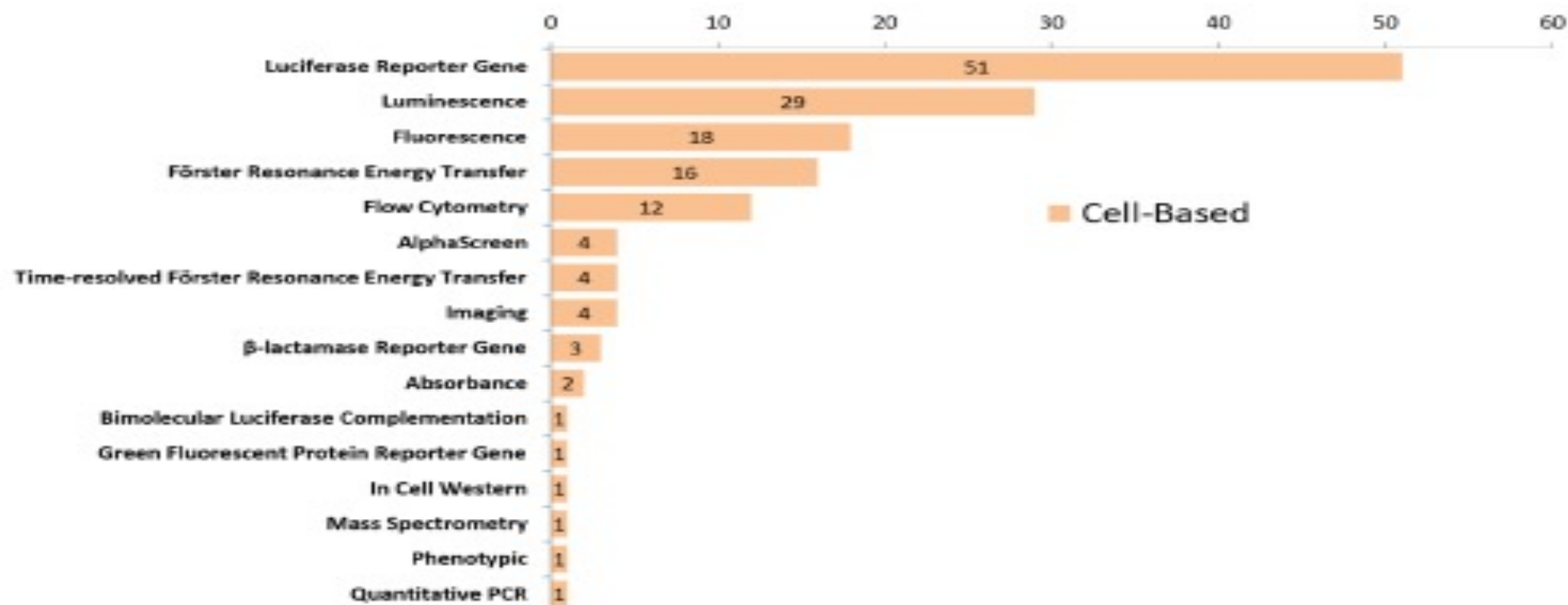
*HTS is a standard step in the drug discovery process but has remained problem-ridden.*



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# Cell based HTS assays

## 149 Cancer Relevant Cell-Based HTS Assays from PubChem



Coussens, N. P., Braisted, J. C., Peryea, T., Sittampalam, S. G., Simionov, A. and Hall, M. D. **Small Molecule Screens: A Gateway to Cancer Therapeutic Agents with Case Studies of FDA-Approved Drugs** *Pharmacological Reviews*, October 2017, 69 (4) 479-496



# Assay choice

## Important Considerations for Choosing an Assay

---

- **Assay expense**
  - Cost per well
  - Disposal cost(s)

# Important considerations

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- **Available instrumentation**
  - Select the best possible assays based on the available instrumentation

# Assay throughput

## Important Considerations for Choosing an Assay

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- **Available instrumentation**
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- **Assay throughput**
  - Miniaturization reduces the cost per well



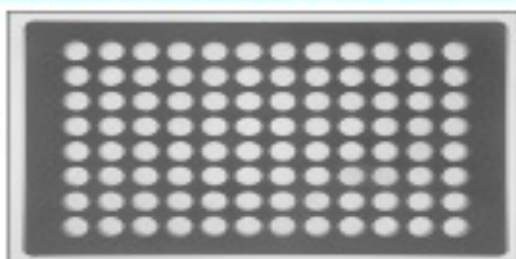
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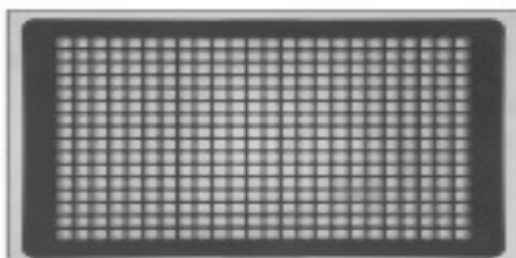
# Assay miniaturization

## Assay Miniaturization Saves Time and Reagents

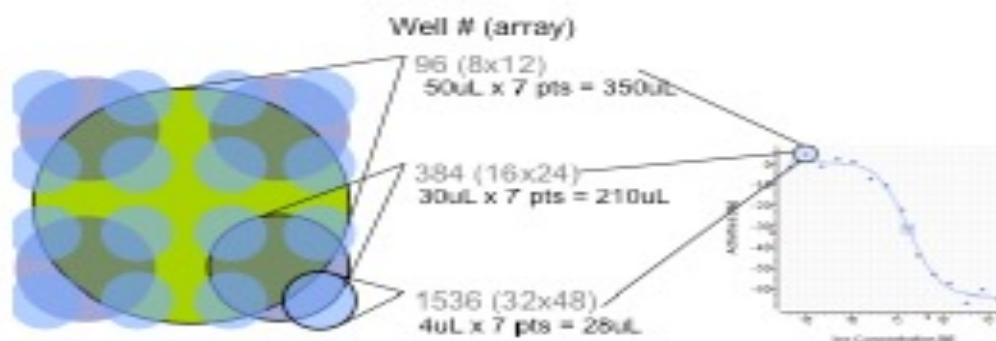
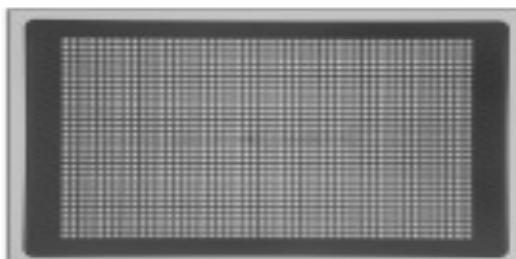
**96-well**  
~50,000 cells/well



**384-well**  
~5,000 cells/well



**1536-well**  
~500 cells/well



	96	384	1536
Plates per 100,000 compounds:	1,042	261	66
Assay volume (µL):	50-200	30-50	2-8
Adherent cell seeding density:	~10,000	~2,000	~500

Jamison, Shane R. 'Conducting High Content Phenotypic Screening: Special Topics in Drug Discovery.' InTech, 2018.



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- **Ability to multiplex**
  - Can the response be measured by a single parameter; is multiparametric output possible?
  - Increased data per sample
  - Can guide hit selection by differentiating selectivity among related targets
  - Can distinguish pathway inhibition from cytotoxicity in a cell-based assay



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- **Reagents**
  - Stability for hours is important
  - Consistency is critical (ideally obtain a large quantity from a single lot)
  - All reagents need to be validated (cell lines, antibodies, enzymatic purity, etc.)

# Important considerations

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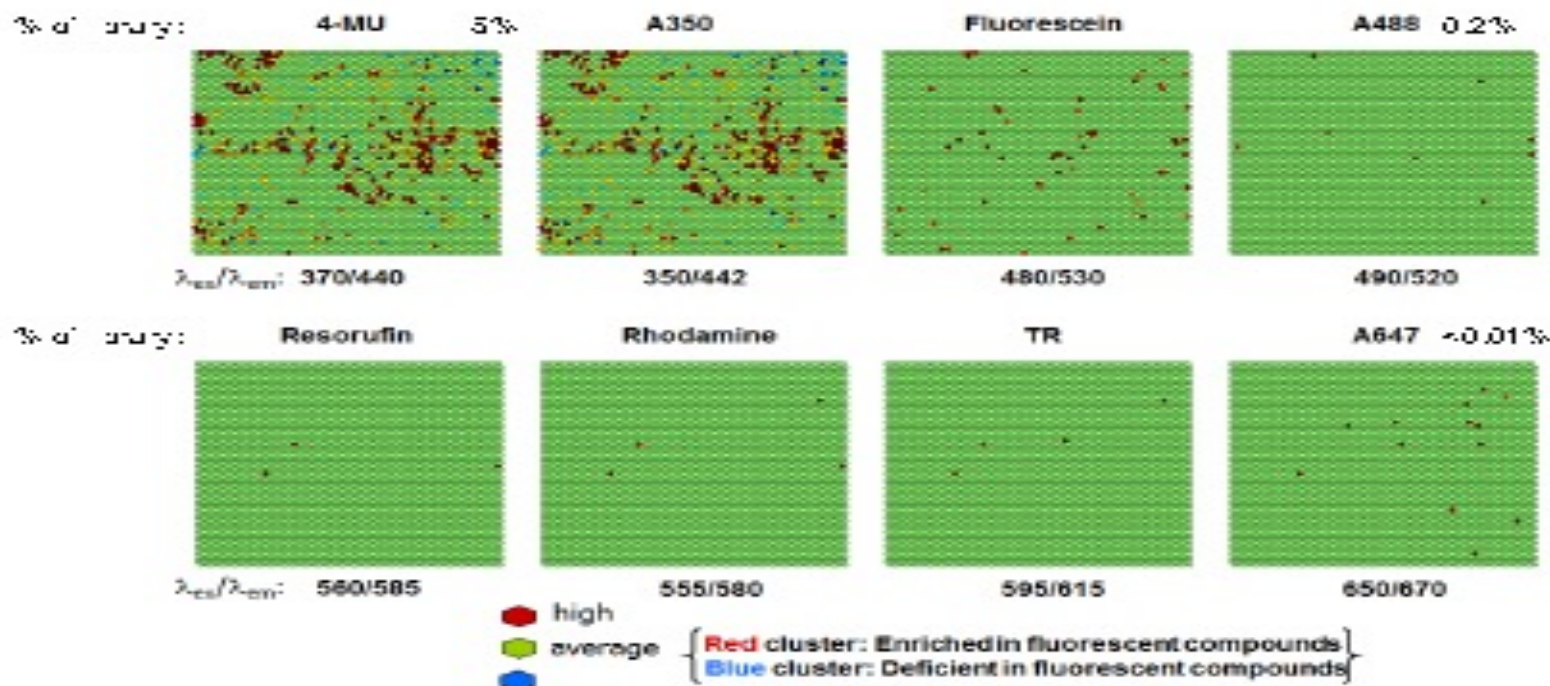
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- **Potential for assay interference**
  - Fluorescent compounds can interfere with fluorescent readouts
  - Colored compounds might interfere with luminescence



# Fluorescence spectroscopic profiling

## Fluorescence Spectroscopic Profiling of Compound Libraries

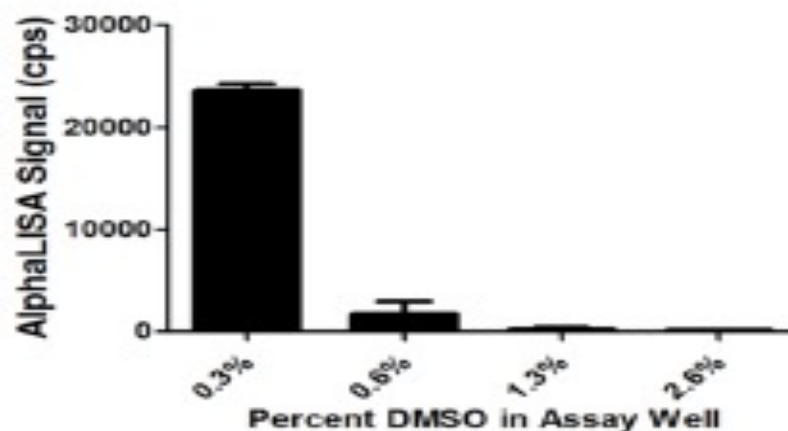
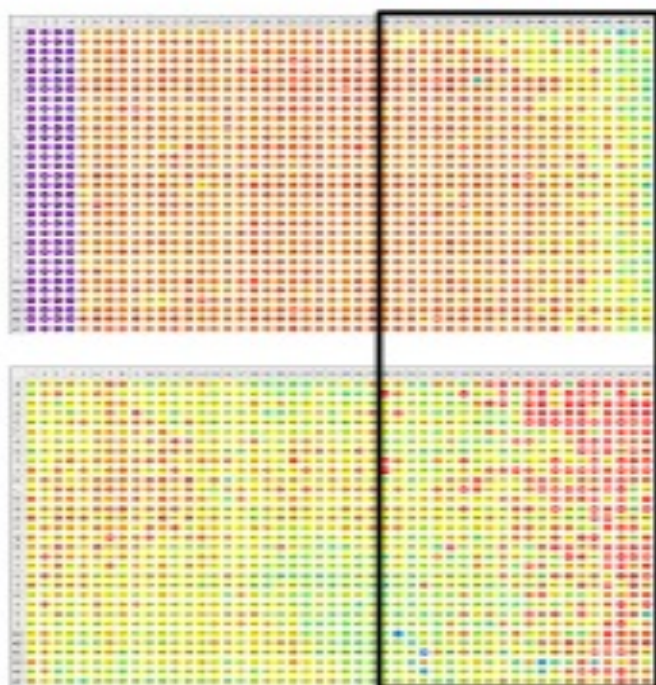


Simionov, A., Jadhav, A., Thomas, C.J., Wang, Y., Huang, R., Southall, N.T., Shinn, P., Smith, J., Austin, C.P., Auld, D.S. and Ingleso, J., 2008. Fluorescence spectroscopic profiling of compound libraries. *Journal of Medicinal Chemistry*, 51(8), 2363-2371.



# Assay tolerance

## Determination of Assay Tolerance to DMSO/Vehicle is Important



Yasgar A., Jadhav A., Simoonov A., Coussons N.P., **AlphaScreen-Based Assays: Ultra-High-Throughput Screening for Small Molecule Inhibitors of Challenging Enzymes and Protein-Protein Interactions**. *Methods Mol Biol.* 2016;1439:77-98.



# Important considerations

## Important Considerations for Choosing an Assay

---

- Homogenous assay format is preferred for screening
  - Add reagents, mix and measure (no solution removal or wash steps)
  - Automation friendly
  - Reduces variability
  - Decreases hands-on time
  - Improves reproducibility

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  - Off-line reagent preparation
  - Is temperature equilibration required
  - Actual assay time
  - Kinetic versus end point read
  - Time required for data analysis and record keeping



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- Signal stability
  - Does the response occur rapidly or within a few minutes or hours?
  - Longer signal stability allows for flexibility in automated systems
  - Longer signal stability minimizes differences among plates within a stack



# Important considerations

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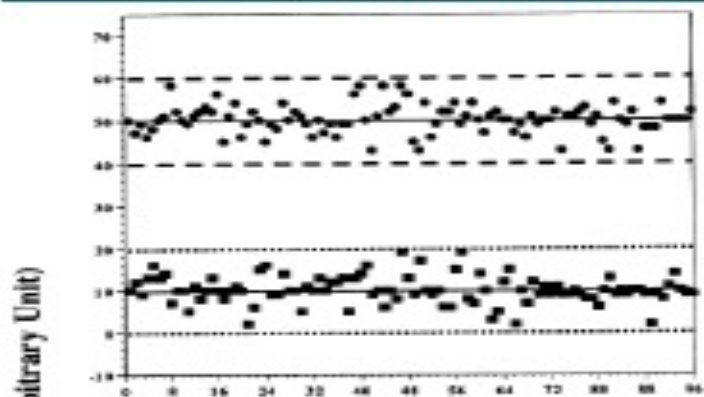
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- **Assay Sensitivity**
  - Choice of readouts is important
    - Colorimetric < fluorescent < luminescent



# Assay suitability

## Evaluating Assay Suitability for Screening



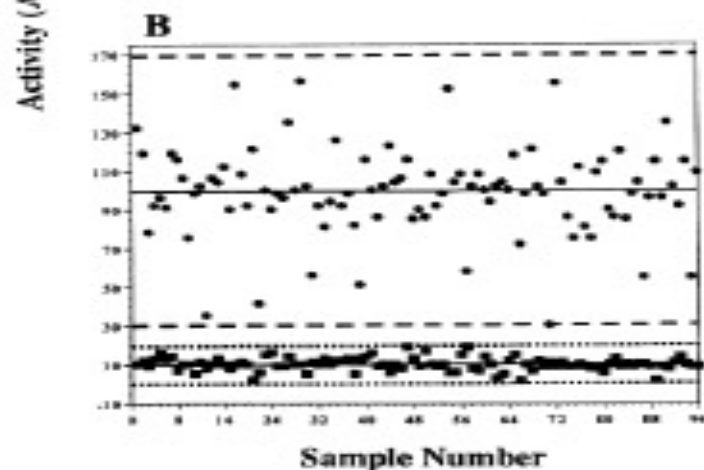
$S/N = 12$

$S/B = 5$

$z = 0.5$

$$S/N = \frac{\text{mean signal} - \text{mean background}}{\text{standard deviation of background}}$$

$$S/B = \frac{\text{mean signal}}{\text{mean background}}$$



$S/N = 27$

$S/B = 10$

$z = 0.1$

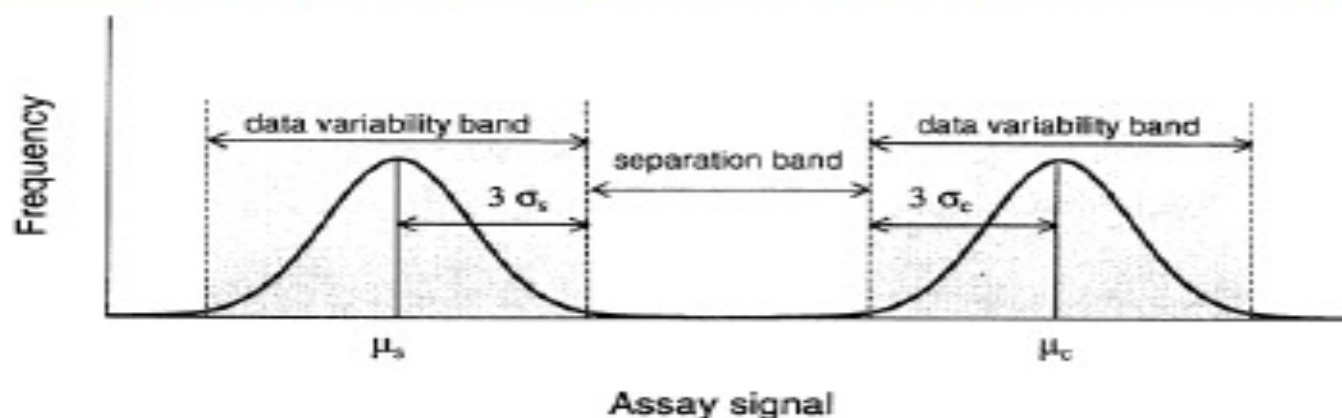
$$Z = 1 - \frac{3SD \text{ of sample} + 3SD \text{ of control}}{|\text{mean of sample} - \text{mean of control}|}$$

A Simple Statistical Parameter for Use in Evaluation and Validation of High Throughput Screening Assays. Zhang JH, Chung TD, Oldenburg KR. J Biomol Screen. 1999;4(2):67-73.



# Assay suitability

## Evaluating Assay Suitability for Screening



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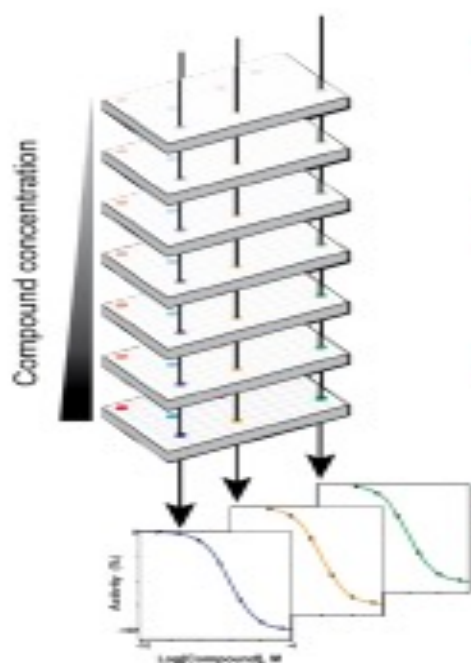
Z-factor value	Structure of assay	Related to screening
1	SD = 0 (no variation), or the dynamic range $\rightarrow \infty$	An ideal assay
$1 > Z \geq 0.5$	Separation band is large	An excellent assay
$0.5 > Z > 0$	Separation band is small	A double assay
0	No separation band, the sample signal variation and control signal variation bands touch	A "yes/no" type assay
<0	No separation band, the sample signal variation and control signal variation bands overlap	Screening essentially impossible

A. B. and S. A. S. C. Parameter for Use in Evaluation and Validation of High Throughput Screening Assays, Zhang L. L. Chung T. D. Odellburg K. L. C. Data Screen. 1999 4(2):67-70.



# Improving early discovery

## Improving the Process of Early Discovery: Quantitative High-Throughput Screening (qHTS)



- Conventional screening done at one concentration
  - Not appropriate for potency testing – “dose makes the poison”
- qHTS tests compounds assayed at **multiple** concentrations (range: 4 logs)
- Enabled by miniaturized assay volumes (2-8  $\mu\text{L}$  per test) and informatics pipeline
- Generates *pharmacological actives* instead of statistical “hits”
  - Dramatically increases reliability
  - Dramatically reduces false positives and false negatives
- *To date, several hundred million datapoints from several hundred screens have been generated and deposited in the public domain.*

# Medicinal chemistry

## Medicinal Chemistry, an Integrated Process



### Tier 1: Synthesis & validation

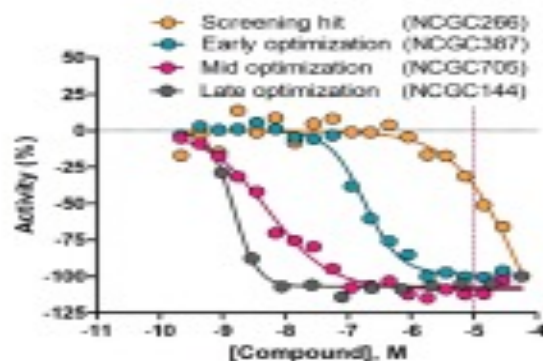
- Medicinal chemistry
- Purification
- In vitro ADME

### Tier 2: Compound profile expansion

- Met ID/ CYP studies
- In vitro toxicology

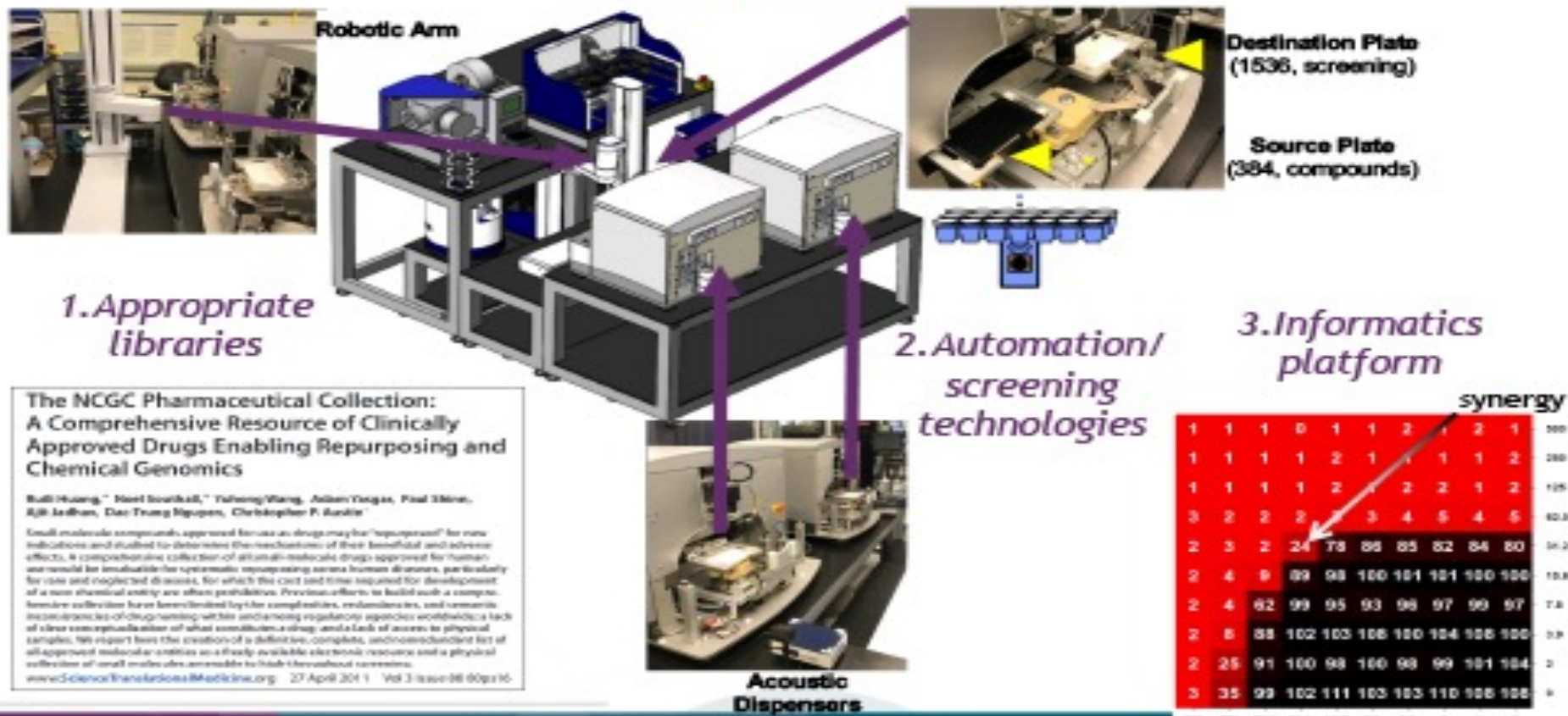
### Tier 3: Advanced Preclinical studies

- Formulation
- Scale-up
- In vivo PK/PD
- Preclinical toxicology



# Drug combinations

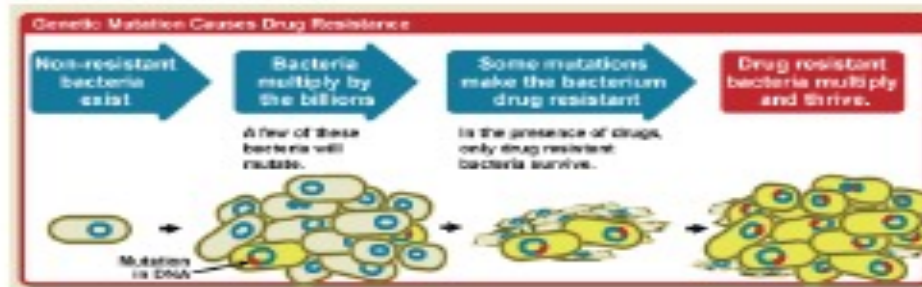
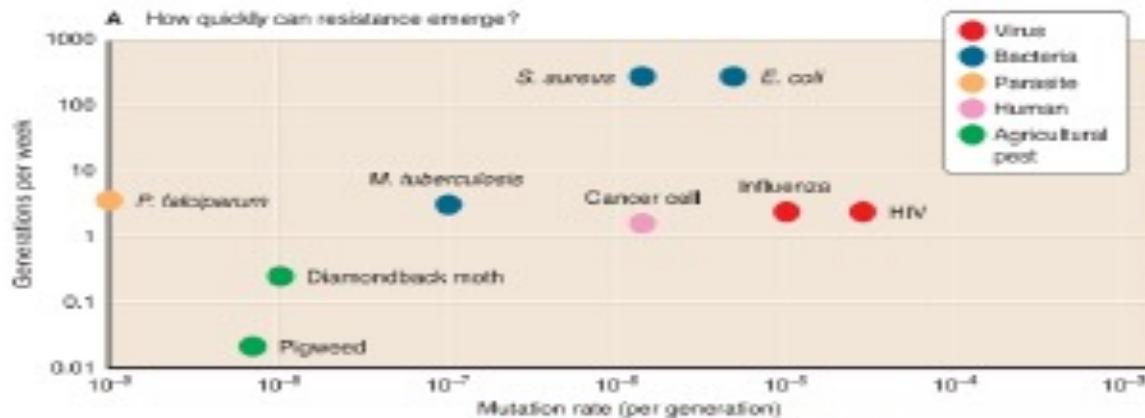
## Translation Challenge: Rapid Discovery of Drug Combinations



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# Resistance

## Application of Drug Combinations to Address Resistance



# Drug resistance

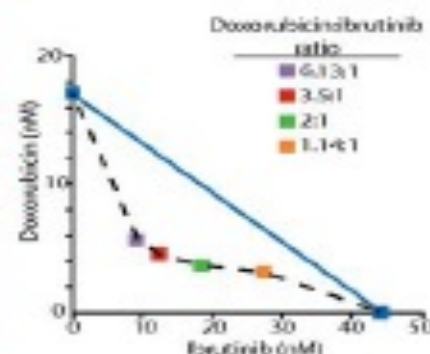
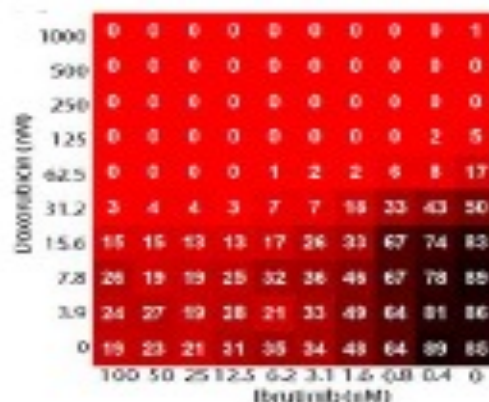
## Dissemination of technology: combination screening to overcome drug resistance in cancer cells

- ABC subtype of Diffuse Large B-Cell Lymphoma (ABC-DLBCL) has poor prognosis and response to treatment
- Ibrutinib is a BTK inhibitor that has activity against ABC DLBCL
- Study evaluated 459 drugs in combination with Ibrutinib
  - » 6 x 6 concentration-response “matrix blocks”, validation in 10 x 10 concentration-response matrix blocks
- DNA-damaging agents identified as synergizing with Ibrutinib in killing ABC DLBCL cell lines
- **Dissemination:**
  - » Protocols
  - » Source code for dispense

High-throughput combinatorial screening identifies drugs that cooperate with ibrutinib to kill activated B-cell-like diffuse large B-cell lymphoma cells

Lesley A. Mathews-Gibson<sup>1,2</sup>, Rajarshi Guha<sup>1,2</sup>, Paul Shien<sup>1,2</sup>, Ryan M. Young<sup>1,2</sup>, Jonathan M. Keller<sup>1,2</sup>, Bongho Uu<sup>1</sup>, Ian S. Goldfarb<sup>1</sup>, Adam Yeager<sup>1</sup>, Crystal McKeighe<sup>1</sup>, Matthew B. Bower<sup>1</sup>, Damien Y. Dumesnil<sup>1</sup>, Jian-Kang Jiang<sup>1</sup>, Sam Michael<sup>1</sup>, Tim Macosko<sup>1</sup>, Wenwei Huang<sup>1</sup>, Martin J. Walsh<sup>1</sup>, Bryan T. Mott<sup>1</sup>, Parasara Patel<sup>1,2</sup>, William Lasker<sup>1</sup>, David A. Wainberg<sup>1</sup>, Christopher A. Leiden<sup>1</sup>, Giuseppe Ruff<sup>1</sup>, Ajit Keshav<sup>1</sup>, Brian D. Pepper<sup>1</sup>, Christopher R. Austin<sup>1</sup>, Scott E. Marder<sup>1</sup>, Anton Simionov<sup>1</sup>, Marc Ferrer<sup>1</sup>, Gail M. Staudt<sup>1,2</sup>, and Craig J. Thomas<sup>1,2</sup>

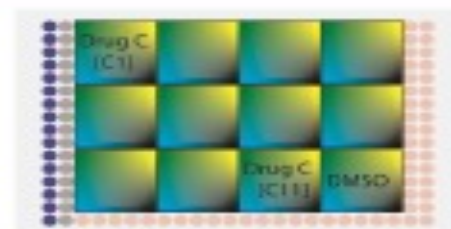
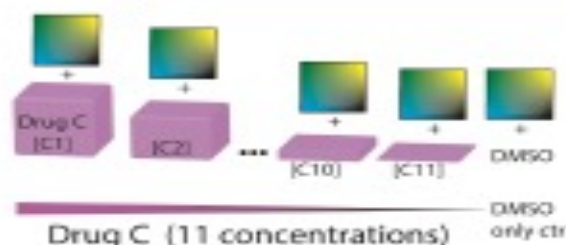
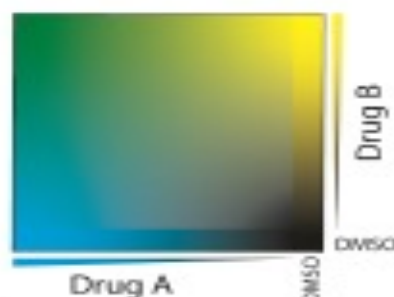
<sup>1</sup>Division of Precision Innovation, National Institutes of Health Chemical Genomics Center, National Center for Advancing Translational Sciences, Biomedical Research Center for Cancer Research, and <sup>2</sup>Translational Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892 and <sup>3</sup>Translational Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892



# Drug combinations

## Example: triple drug combination screening to tackle resistance against artemisinin-based combination therapies in malaria

ACS Pharmacol. Transl. Sci. 2020, <https://dx.doi.org/10.1021/acscptsci.0c00110?ref=pdf>



- Drugs A and B are acoustically dispensed in a 10x10-well matrix, 12 replicate blocks per plate. Single drug responses, bottom row (Drug A) and right column (Drug B).

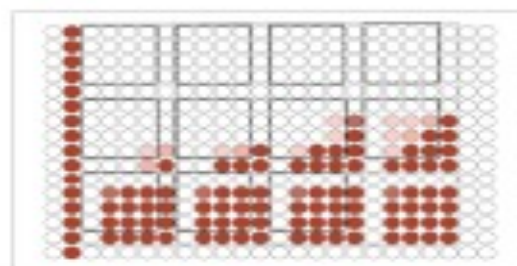
- To each replicate block, serial dilutions of Drug C is acoustically dispensed, with the final block serving as a DMSO control

- Plate view of triple combination screening plate with positive control (artesunate, blue) and neutral controls (DMSO, grey) also shown.

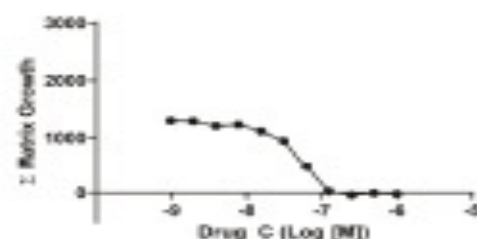


- Dispense *P. falciparum* and erythrocytes, incubate 72 hr

- Dispense 2  $\mu$ L of SYBRGreen1 and lysis solution, incubate overnight. Fluorescence quantified



- Parasite proliferation response is normalized to artesunate and DMSO controls. For each concentration Drug A + Drug B wells is summed.

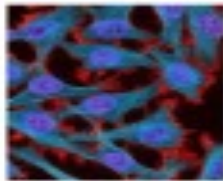


- Triple drug response is analyzed as a function of Drug C concentration.

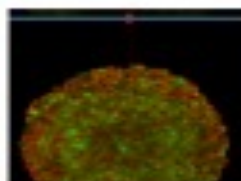
# 3D models

## Increasing the predictivity of *in vitro* assays: a continuum of 3D models of healthy and diseased tissues

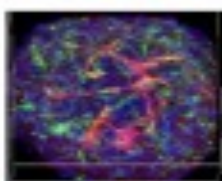
2D



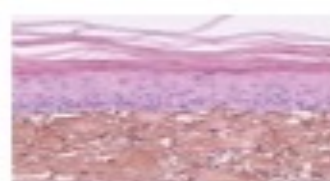
Spheroids



Organoids



Printed Tissues



Organ-on-a-chip



HTS compatibility

Physiological complexity

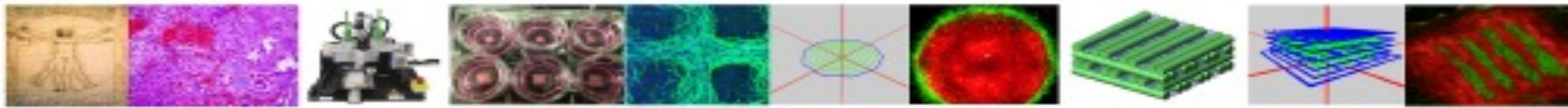


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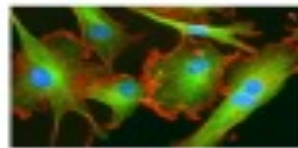
# Tissue bioprinting

## 3D Tissue Bioprinting



Gel

+



Cells

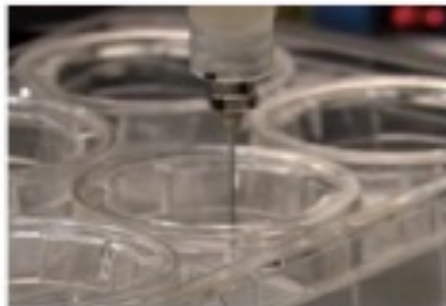


Syringe



Printer

Hydrogel polymer is mixed with cells and loaded into syringe.



The printer "3D prints" the cell/gel mixture in a layer by layer approach.



Printed construct



1 day



1 week



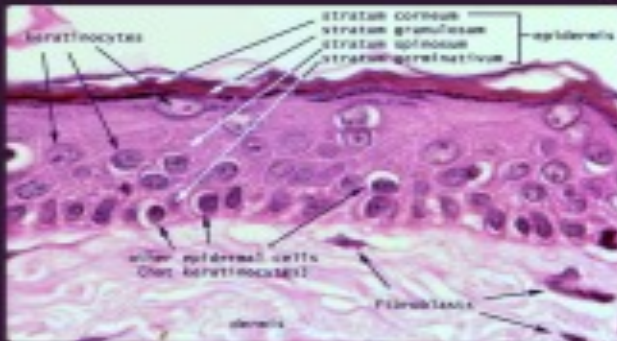
2 weeks

The printed construct is incubated to allow the cells to form a tissue, and to enable proper cell differentiation.

# Epidermis Functional activity analyses. Stem cell technologies

## Layers of the Epidermis: native skin *versus* 3D-bioprinted skin

### Native Skin



<http://www.siumed.edu/~eking2/intro/IN005b.htm>

### 3D-Bioprinted Skin



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# Bioprinted skin

## Generation of bioprinted skin tissues

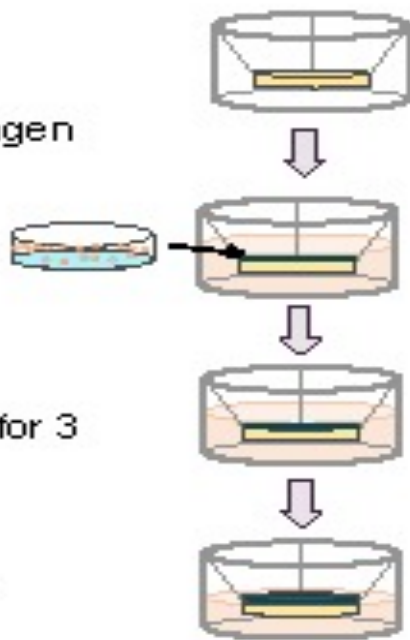
### Reconstructed human epidermis (RhE)

1. Coat the 96-well transwell insert membrane with collagen

2. Add keratinocytes

3. Submerge culture for 3 days

4. Air-liquid interface culture for 8 days



2. Bioprint fibroblast bioink to a 3-layer U shape on bottom side of 96-well transwell insert membrane

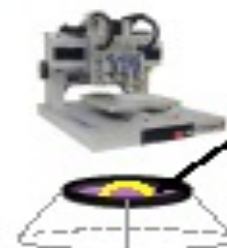
4. Submerge bioprinted tissue in medium for 7 days

5. Add keratinocytes and submerge culture for 3 days

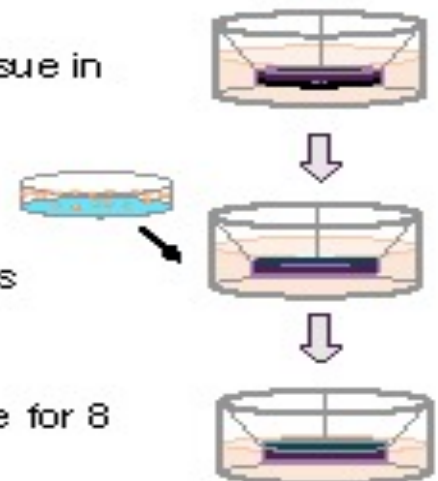
6. Air-liquid interface culture for 8 days

### Full thickness skin tissue (FTS)

1. Suspend fibroblasts in bioprinting gel



3. Add bioprinting gel to cover the U shape



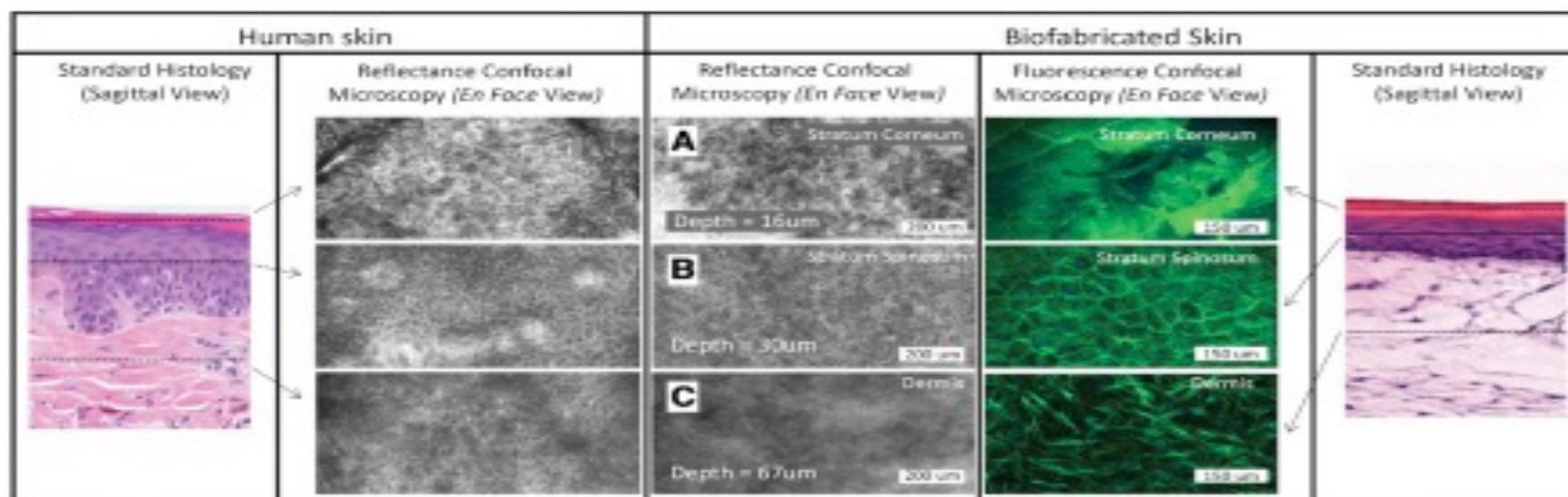
# 3D Tissue model

www.oncotarget.com

Oncotarget, 2020, Vol. 11, (No. 27), pp: 2587-2596

Research Paper

**A 3D biofabricated cutaneous squamous cell carcinoma tissue model with multi-channel confocal microscopy imaging biomarkers to quantify antitumor effects of chemotherapeutics in tissue**



Collaboration between NCATS (Marc Ferrer) and Rockefeller University (Daniel Gareau)



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# Assay development

**Where do I go for more  
information about assay  
development?**



# Assay guidance manual

## Sharing internal know-how: Assay Guidance Manual (47 chapters/ 1,338 printed pages)



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Assay Technologies	2 Chapters
Instrumentation	2 Chapters
Pharmacokinetics and Drug Metabolism	1 Chapter
Glossary of Quantitative Biology Terms	1 Chapter

<https://ncats.nih.gov/agm-video>

### Assay 2<sup>nd</sup> Video

1. Assay 2, CP: Welcome to the Assay Guidance Manual (AGM) Workshop
2. Carosons, NP: Strategies for Assay Selection & Robust Biochemical Assays
3. Ass, J: Treating Cells as Reagents to Design Reproducible Screening Assays
4. Fung, Q: Assay Development Considerations for High Content Imaging
5. Au, D: Studies in Interference and Methods in Assay Interference
6. Doherty, J: Assay Interference by Chemical Reactivity
7. Chung, J: Basic Assay Statistics, Data Analysis & Rules of Thumb
8. Damschke, W: Reproducibility & Differentiability of Potency Results
9. Swamynathan, G: Avoiding Artifacts & Interference in Assay Operations

### Assay 2<sup>nd</sup> Video

1. Assay 2, CP: Welcome to the Assay Guidance Manual (AGM) Workshop
2. Carosons, NP: Robust Assays Define Success in Preclinical Research
3. Huang, M: Target Identification & Validation in Translational Discovery
4. Foley, T: Development & Validation of Cell-Based and Biochemical Assays
5. Ass, J: Treating Cells as Reagents to Design Reproducible Screening Assays
6. Fung, Q: Assay Development for HCS & Best Practices for 3D HCS
7. Roth, C: Mass Spectrometry for Drug Screening and Lead Optimization
8. Doherty, J: Bioassay Interference by Aggregation and Chemical Reactivity
9. Fung, Q: Lead Selection and Optimization by Medicinal Chemistry
10. Fung, M: In Vitro Technological Testing Using a qHTS Platform
11. Fung, M: In Vitro Assessment of ADME Properties of Lead Compounds
12. Calkins, D: Statistical Design of Experiments for Assay Development
13. Gupta, R: Pharmacokinetics to Target Evaluation and Drug Discovery
14. Wodner, J: Assay Operations: Keeping Assays Robust and Reproducible

Website: <https://ncats.nih.gov/exportofpreclinicalassays>

Email us: [NCATS\\_AGM\\_Editorial@mail.nih.gov](mailto:NCATS_AGM_Editorial@mail.nih.gov)



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# AMG workshop



## AGM Workshop on DNA-Encoded Libraries for Lead Discovery

September 1, 2021 – September 2, 2021  
Virtual (All times are in ET)

### AGENDA: Day 1

- |          |   |
|----------|---|
| 12:30 PM | <b>Opening Remarks</b><br>Anton Simeonov, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH) |
| 12:45 PM | <b>Introduction and Overview of Workshop</b><br>Timothy L. Foley, Pfizer Inc.   |
| 1:00 PM  | <b>Opening Talk: DNA-Encoded Chemical Libraries: From the Bench to the Clinic</b><br>Dario Neri, ETH Zürich and Philogen                    |

<https://ncats.nih.gov/expertise/preclinical/agm/training>



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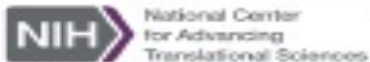
# Response to Covid-19

## Response to COVID-19: OpenData Portal enables data and protocol sharing in near-real time

U.S. Department of Health and Human Services

National Institutes of Health

National Center for Advancing Translational Sciences



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OpenData Portal

Home

OpenData Browser

Assays

Animal Models

Omics Efforts

Highlights

Resources

### OpenData | COVID-19

NCATS is generating a collection of datasets by screening a panel of SARS-CoV-2-related assays against all approved drugs.

These datasets, as well as the assay protocols used to generate them, are being made immediately available to the scientific community on this site as these screens are completed.

<https://opendata.ncats.nih.gov/covid19/>



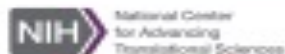
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# Open data portal

The screenshot shows the NIH OpenData Portal interface. At the top, there are navigation links for Home, OpenData Browser, Assays, Animal Models, Omission Effects, Highlights, and Resources. Below these is a search bar with the text 'MOA, (S2) gene, sample/drug' and a dropdown menu set to 'Approved Drug Collection (NDC)'. The main content area is a heatmap titled 'Drug Information' and 'Viral Entry'. The heatmap has columns for various viral entry and replication stages, including 'Viral Entry', 'Viral Replication', 'In vitro infectivity', 'Live virus infectivity', and 'Human cell toxicity'. The rows list various drugs, including Botulin, Tyrosine acid, Methoxyisoxanthine, and Mithoxanthine. A red arrow points to the 'Approved Drug Collection (NDC)' dropdown menu. The heatmap cells are colored in shades of green, yellow, and red, indicating different levels of interaction or toxicity.

# Open data portal

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## OpenData Portal

[Home](#)[OpenData Browser](#)[Assays](#)[Animal Models](#)[Omics Efforts](#)[Highlights](#)[Resources](#)

### SARS-CoV-2 Assays

The assays below have been developed to cover a wide spectrum of the SARS-CoV-2 life cycle, including both viral and human (host) targets, and are updated continuously as more assays are developed and screened, and all protocols and screening datasets will be made freely available to the community.

Assay Name --	Assay Type --	Target Category --	Detection Type --	Cell Line --	Status --
<a href="#">Spike-ACE2 protein-protein interaction (AlphaLISA)</a>	Proximity	Viral Entry	AlphaLISA		Screening
<a href="#">Spike-ACE2 protein-protein interaction (Triton CounterScreen)</a>	Proximity	CounterScreen	AlphaLISA		Screening
<a href="#">Spike-ACE2 protein-protein interaction (SPR)</a>	Proximity	Viral Entry	High-content imaging		Under dev
<a href="#">Spike-ACE2 binding</a>	Binding	Viral Entry	Geo-Laser Interferometry		Screening
<a href="#">ACE2 binding</a>	Biophysical	Viral Entry	Interferometric Nanoscale Thermoplasmonics		Screening
<a href="#">ACE2 enzymatic activity</a>	Biochemical	Enzyme Activity	Fluorescence		Screening
<a href="#">SARS-CoV-2 RNA detection</a>	Cell Culture	RNA Detection	RT-qPCR		Screening

All experimental protocols are being shared openly on the site to allow others to run them

# Learn More About NCATS



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